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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,706	02/09/2004	Lester F. Lau	05031.0008.NPUS01	2022

7590 02/22/2007

HOWREY SIMON ARNOLD & WHITE LLP
Attention: Patent Administrator
Box No. 34
1299 Pennsylvania Avenue, N.W.
Wahington, DC 20004-2402

EXAMINER	
POPA, ILEANA	
ART UNIT	**PAPER NUMBER**
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/774,706	LAU, LESTER F.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,10,16,19 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,10,16,19 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Upon further consideration, the finality of the rejection of the last Office action is withdrawn. However, new grounds of rejection are made, as shown below.

2. Claims 2, 3, 5-9, 11-15, 17, 18, and 20 have been cancelled. Claims 1, 10, 16, and 19 have been amended.

Claims 1, 4, 10, 16, 19, and 21 are pending and under examination.

Claim Rejections - 35 USC § 112, enablement

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 19 and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC § 112, first paragraph, have been described by the court in *In re Wands,* 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or

guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skills of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided.

The instant claims are drawn to (i) a method of identifying a modulator of symptoms associated with atrioventricular septal defects (AVSDs) comprising contacting a $CCN^{+/-}$ mouse with a suspected modulator and measuring the effect that the suspected modulator has on the phenotype associated with atrioventricular septal defects in comparison to the control, and (ii) a method of identifying an animal that is predisposed to AVSDs by detecting the presence of an alteration in one or more alleles of the *CCN1* gene in a DNA sample isolated from the animal.

The instant specification teaches by exemplification (i) method of obtaining $CCN^{+/-}$ mice, wherein the method consists of inactivating the *CCN1* gene by inserting a targeting construct comprising β-*gal* and *neo* coding regions, and (ii) characterizing the cardiovascular defects of the $CCN^{+/-}$ embryos. The above evidence has been noted and considered. However, the instant specification is not enabled for the presently claimed invention for the reasons discussed below.

Applicant contemplates to (i) use the $CCN^{+/-}$ mice to identify an agent capable of modulating AVSDs and (ii) to genetically screen for animals that are predisposed to develop AVSDs. However, with the exception of $CCN^{+/-}$ mice, wherein the

heterozygous mutation consisting of the complete elimination of one of the *CCN1* allele leading to AVSD development, the specification does not disclose, and the art does not teach any correlation between mutations in the *CCN1* gene and the development of AVSDs in any animal, nor do they teach that elimination of one or both *CCN1* alleles is a naturally occurring mutation leading to AVSD. Just because such a mutation results in a phenotype in an experimental animal model does not in itself render the animal model useful for identifying agents that could modulate the development of AVSD (claim 19) because (i) such a drastic mutation is not naturally occurring, and (ii) the phenotype may not be due to the disruption of the gene itself. Thus, Maslen (Curr Opin Cardiol, 2994, 19: 205-210) teaches:

> "Indeed, there are a number of genetically modified mice that have ACSD as part of their phenotype. But do these experimental systems reflect the pathogenesis of heart defects in humans? Actually, it is doubtful that most genetic knockout and gene ablation studies are directly analogous to the genetic etiology of heart defects in humans. Although these studies do a marvelous job of identifying the function of genes during development, the models are usually created by introducing severe genetic abnormalities such as complete elimination of gene expression, often resulting in embryonic lethality. Consequently, the results may not be directly relevant to the genetic basis of AVSD in humans. Nevertheless, to advance our understanding of AVSD, we must take advantage of the information obtained from animal and biochemical studies. In the final analysis, this may require a simple but tedious look-and-see approach to determine which genes are associated with AVSD in humans. The challenge will be interpreting the data, because it is unlikely that the associated mutations or polymorphisms will have obvious devastating effects on gene expression or protein structure or function."

And, Scarff et al. (Genesis, 2003, 36: 149-157, Abstract, p. 155, columns 1 and 2) teach that using transgenic mice to identify the function of a knockout gene might be misleading because the phenotype may be a result of the retention of the selectable marker gene (i.e., the *neo* gene) in mice, which affects expression of neighboring

genes, i.e., the observed phenotype may not be a result of the disruption of the gene itself:

> "It is becoming apparent that retention of the selectable marker gene in knockout mice can lead to a confounding phenotype. In most cases the retained selectable marker gene affects the expression of neighboring genes."

Hence, from the nature of the invention, one of skill in the art would nor *a priori* know that an agent identified by using the claimed mouse model could be used to modulate AVSD in animals in general because the $CCN^{+/-}$ mouse model does not represent the genetic etiology of the disease in animals. One of skill in the art would know that the use of such an agent to modulate AVSD would be unpredictable and would require undue experimentation to practice the instant method, as claimed.

Regarding the method of diagnosing (claim 21), it is noted that Applicant broadly claims that any alteration in one or more allele of the *CCN1* gene could be used to identify an animal predisposed to AVSDs. While it is true that the prior art teaches transgenic mice with a complete disruption of the *CCN1* gene in one or more allele, the prior art teaches the use of such mice to study CCN1 function during the development of the vascular and skeletal systems and not for the drug discovery (see Mo et al., Mol Cell Biol, 2002, 22: 8709-8720, Abstract, p. 8709, column 2 bridging p. 8710, p. 8719, column 1; of record). Just because the complete absence of CCN1 function leads to abnormal development of the vascular system in an artificially created animal model, does not mean that alterations in the *CCN1* gene are the cause of AVSDs. Even assuming, for the sake of the argument that the *CCN1* gene would be identified as the cause of AVSDs, not any alteration would necessarily result in predisposition to AVSDs.

However, neither the specification nor the art teach any naturally occurring alteration of the *CCN1* gene that results in AVSDs in any animal. There is no reference or guidance to what type of alteration one of skill in the art should look for. Except for the artificial, complete disruption of one or more *CCN1* alleles, there is no other alteration one of skill in the art would associate with AVSD. Beside the artificially created mouse there is no indication of a naturally occurring alteration in the *CCN1* gene associated with AVSDs and Applicant did not provide any example of such alteration. The art teaches that (i) there is an extensive genetic heterogeneity for AVSDs and that AVSDs occur as a clinical feature of several distinct syndromes or as sporadically occurring malformations, (ii) the different syndromes manifesting AVSD, such as Down syndrome, Ivemark syndrome, or Ellis-van Creveld syndrome, to enumerate a few, are caused by genes other than *CCN1* and these genes, not *CCN1* are the primary genetic defect that leads to AVSDs, and (iii) in the case of sporadically occurring AVSDs, the art clearly teaches a multifactorial origin with multiple genes simultaneously involved, with many of these genes identified as susceptibility genes, but none shown to be causal or associated with sporadic AVSD (Maslen, p. 205, columns 1 and 2, p. 206, columns 1 and 2, p. 207,column 1 and 2). Given these teachings, one of skill in the art would not recognize that screening for alterations in the *CCN1* gene would identify an animal predisposed to AVSD. One of skill in the art would require undue experimentation to determine which alteration, if any, is correlated with predisposition to develop AVSD.

In conclusion, the specification does not provide enablement for a method of identifying a modulator of the development of AVSDs by using $CCN^{+/-}$ mice or for a

method of identifying an animal that is predisposed to AVSDs by detecting alterations in one or more allele of the *CCN1* gene.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims1, 4, 10, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Mo et al. (Mol Cell Biol, 2002, 22: 8709-8720, of record).

Mo et al. teach a method of producing, identification, and isolation of transgenic mice (and embryos) whose genome comprise heterozygous or homozygous disruptions of the CCN1 gene, and testing the transgenic mice for their genotype (claims 1, 4, and 10) (p.8710, column 2, bridging p.8711, Table 1). Although Mo et al. do not mention the phenotype of the heterozygous mice, the heterozygous disruption in the CCN1 gene must necessarily have resulted in the claimed AVSDs, i.e., the phenotype is inherent to the transgenic mice comprising a heterozygous or homozygous disruption in the CCN1 gene. With respect to the limitation of testing the heterozygous transgenic mice for a phenotype associated with atrioventricular septal defects (claim 16), it is noted that there is no requirement for the defect to be detected. Mo et al. teach analyzing β-galactosidase expression in heterozygous mice expressed by in situ hybridization and immunocytochemistry (p. 8710, column 2, second paragraph), which would necessarily

have resulted in the determination of AVSD and therefore meets the limitations of claim 16 to the extent that the mouse is analyzed (it is noted that AVSD is a prominent phenotype that cannot be missed when analyzing β-galactosidase expression by immunocytochemistry). Since Mo et al. teach all the limitations of the instant claims, the claimed invention is anticipated by the above-cited art.

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

Joe Woitach
AU1633